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Histoepidemiological Study of Prostatic Epithelial Metaplasia's Association in Transurethral Resection of the Prostate

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The study examined the relationships and associations of selected pathological features (prostatic epithelial metaplasia – PEM) in a single transurethral resection of the prostate (TURP) material. An additional immunohistochemical investigation with p63 was made. PEM was found in 60.6% : squamous metaplasia in 11.5%; urothelial metaplasia in 27.9%; mucinous metaplasia in 4.9%; eosinophilic metaplasia in 55.7% and basal cell hyperplasia (BCH) in 39.3%. All the cases with PEM (100%) are associated with benign prostate hyperplasia (BPH) and variable degree of histologic prostatitis (HP). Expression of p63 is found in all investigated cases in all types of PEM and BCH.

This is the first attempt to investigate the associations between PEM in the context of basic pathology in TURP-material and enrich the available information about the histoepidemiology of prostatic metaplasias. The observed combination between PEMs and their association with BPH and HP in 100% probably reflects the final stage of a single morphogenetic chain.

Key words: prostate, metaplasia, transurethral resection, prostatitis.

Introduction

Metaplasia is a reversible change in which one adult cell type is replaced by another adult cell type, related to the first one [13]. It is a sign of tissue adaptation towards changed conditions or requirements to them.

The prostatic epithelium has an interesting but limited repertoire of responses against injury. These responses include a variety of metaplastic and proliferative lesions that may mimic prostatic adenocarcinoma (PCa) [1].

Prostatic epithelial metaplasia (PEM) is usually a secondary to inflammation, alteration in the hormonal milieu, or injury. The most common lesions in the everyday practice of the pathologists are – four major categories of PEM (squamous, urothelial, mucinous and eosinophilic) and basal cell hyperplasia (BCH). The diagnostic significance of PEM resides in its pseudoneoplastic status, but these metaplastic proliferations are not precursors for prostatic carcinoma [1, 9].

The frequency of PEM, investigated in specimens of prostatic needle biopsies, total prostatectomies, transurethral resection of the prostate (TURP) and autopsies, have been described up to now [1, 9]. Less well studied is their combination with benign prostatic hyperplasia (BPH) and National Institutes of Health (NIH) – category IV prostatitis (so-called histologic prostatitis (HP)) [1, 9, 12, 15].

No studies about the association of PEM in series of a single prostate specimen (TURP) are available so far.

The aim of the current investigation is to examine some histoepidemiological relationships of PEMs in the patient population from a general hospital, in the context of the basic prostate pathology (BPH, HP, PCa and BCH) in TURP-material.

Materials and Methods

A retrospective record review was performed on 61 TURP – specimens obtained at St. George University Hospital of Plovdiv, Bulgaria for the period of one year (2014). The study was approved by the Ethics Committee of the hospital. The age of the patients ranged from 54 to 88 years (mean 72.2 years). The leading clinical symptoms covered the so-called prostatic syndrome typical for BPH and represented a basic indication for surgical intervention. Neither radiation and hormonal treatment nor prostatic surgery and cryosurgery before TURP were performed. All specimens were routinely fixed in 10 % buffered formalin and embedded in paraffin for histological evaluation. Tissue sections from 1 to 10 paraffin blocks for each case, stained with hematoxylin-eosin (HE) and hematoxylin-phloxine-saffron (HPS), were examined retrospectively independently by two pathologists (MK and DD).

Simultaneously, BPH, PCa, HP [12, 14], and BCH were also evaluated. 3 cases of each PEM type and BCH were selected (15 in total). Standard 4-µm-thick consecutive tissue sections were cut and stained immunohistochemically with p63 (clone 4A4 ready-to-use; Ventana Medical Systems, Tucson, AZ).

Results

PEM is found in 37/61 cases (60.6%), localized in the transition zone of the prostate, seen in all investigated TURP specimens. Squamous metaplasia was detected in 7/61 (11.5%) cases. The changes may be focal or diffuse, appearing as intraductal syncytial aggregates of flattened cells with abundant eosinophilic cytoplasm or cohesive aggregates of glycogen-rich clear cells with shrunken hyperchromatic nuclei (**Fig.1A**). Keratinization is unusual except at the edge of infarcts or areas of acute inflammation. When it is in a combination squamous metaplasia is associated most commonly with urothelial metaplasia in 3/7 (42.8%) cases. Urothelial metaplasia was detected in 17/61 (27.9%) cases. Urothelial metaplasia occurs in the medium-sized and small ducts in the prostate beyond the normal transitional-columnar junction that apparently arises as a result of metaplastic change. It is difficult to identify because of variable location of the normal transitional-columnar junction. Microscopically, usually only a few glands are involved in a single focus, but extensive involvement may also be observed. The glands exhibit proliferation of elongated urothelial cells beneath a bland-appearing luminal secretory cell layer (**Fig. 1B**). When it is in a combination urothelial metaplasia is associated most commonly with squamous metaplasia, in 3/17 (17.6%) cases.

Mucinous metaplasia was detected in 3/61 (4.9%). Mucinous metaplasia refers to clusters of tall columnar cells or goblet cells with cytoplasm filled with blue-grey

mucin PAS/alcian blue positive that are infrequently observed in the prostatic acinar epithelium (**Fig. 1C**). We do not observe a combination of this type of metaplasia with another type.

Eosinophilic metaplasia was detected in 34/61 (55.7%) (consistent with previous studies) [11]. The apical portions of secretory epithelial cells were filled with eosinophilic cytoplasmic granules with different size (**Figs. 1D and 2A**). In 13/34 (38.2%) it is a separate process. Eosinophilic metaplasia is combined with urothelial metaplasia in 17/34 (50%), with squamous metaplasia in 7/34 (20.6%) and with BCH in 24/34 cases (70.6%)

Fig. 1A

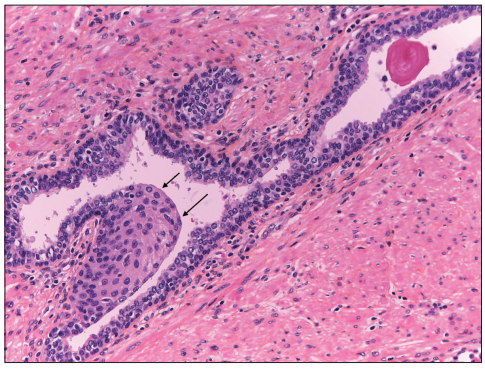

Fig. 1B

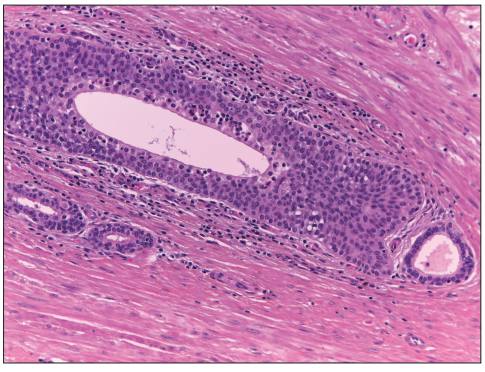

Fig. 1C

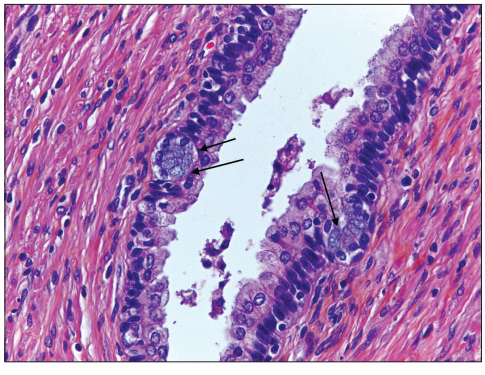

Fig. 1D

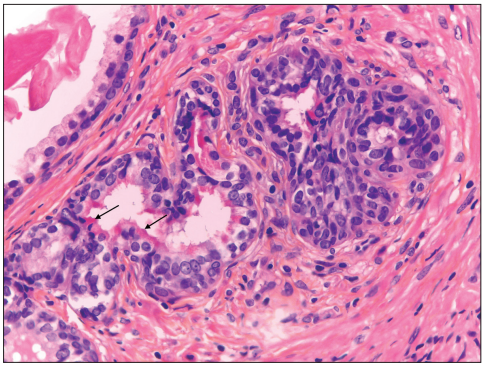

Fig. 1. Prostatic epithelial metaplasia: **(A)** Squamous metaplasia in ductal secretory epithelium on the left side of the image (arrows). **(B)** Urothelial metaplasia in ductal/secretory epithelium; moderate peri- and intra-glandular chronic histologic prostatitis are also observed. **(C)** Mucinous metaplasia (arrows) in ductal secretory epithelium. **(D)** Eosinophilic metaplasia is found in ductal and acinar structures on the left side of the image (arrows) in association with basal cell hyperplasia on the right side of the image: Hematoxylin-phloxine-saffron, (A) and (B) x200; (C) and (D) x400.

BCH was detected in 24/61 (39.3%). In all cases with BCH (100%), it is combined with other type PEM: with squamous metaplasia in 7/24 cases (29.2%), with urothelial metaplasia in 8/24 cases (33.3%), and with eosinophilic metaplasia in 24/24 cases (100%).

The coincidence of quadriple lesion: triple PEM (squamous, urothelial and eosinophilic) and BCH was observed in 3/61 cases (4.9%) (**Fig. 2A**).

Expression of p63 is found in all investigated cases and in all types of PEM and BCH (**Fig. 2B**). Both BCH and HP (of moderate to high grade with glandular, periglandular and stromal localization) were noted in all cases of PEM (100%) (**Figs. 1B and 2A**). There is no association with PCa.

Fig. 2A **Fig. 2B**

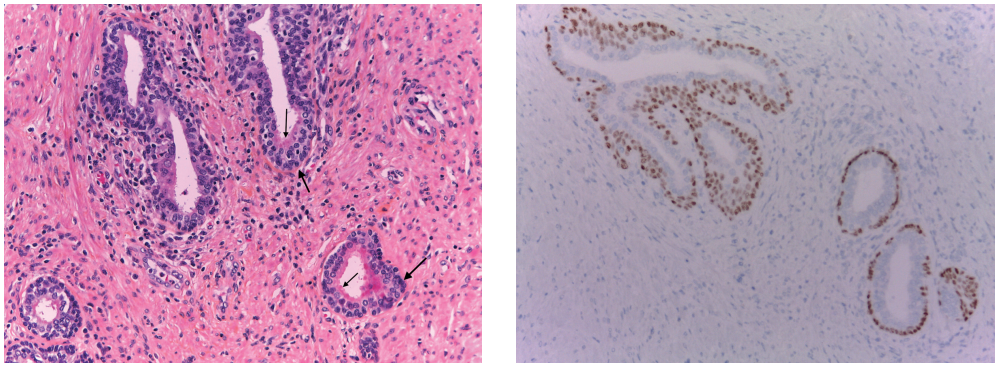

Fig. 2. Prostatic epithelial metaplasia's association in a serial sections: (**A**) Association between eosinophilic metaplasia (thin arrows) and basal cell hyperplasia (thick arrows); moderate periglandular chronic histologic prostatitis are also observed. (**B**) p63 expression in a focus of eosinophilic metaplasia (on the right side of the image) and basal cell hyperplasia (on the left side of the image): (A) Hematoxylin-phloxine-saffron, ×200 and (B) immunohistochemistry anti-p63, x200.

Discussion

Throughout adult life, new developmental commitment of adult stem cells causes frequent metaplastic conversion in some organs. These reversible epithelial replacements are almost always observed in association with chronic inflammation and persistent irritation [8].

Inflammatory mediators (cytokines) and other soluble factors released by both epithelial and inflammatory cells might alter the transcription-factor expression profile of stem cells and lead to the development of metaplasia [8].

The frequency of PEM varies from 0.6 (urothelial) to 94% (squamous metaplasia) depending on the material being investigated [1, 9].

Our results on TURP-specimens confirm this frequency, as we find PEM and BCH in 60.6% and 39.3% of TURP-cases.

Additionally, we show that the associations between different types of PEM is a frequent finding in TURP-specimens. On the other hand, PEM is associated always with BPH, HP and BCH.

PEM and BCH results from a variety of insults to the prostate, including acute and chronic inflammation, infarction, radiation therapy, and androgen deprivation therapy [15].

Squamous metaplasia commonly involves the prostatic urethra in patients with an indwelling catheter. It is a specific phenotype in response to estrogen, and ER α is required to mediate this response [2]. Also, transitional metaplasia may occur in the medium-sized and small ducts in the prostate, sometimes in association with inflammation [15].

Mucinous metaplastic cells in the prostate were found in the foci of atrophy, urothelial cell metaplasia, BCH and BPH [7]. In our single case, we did not find any combination with other types of PEM.

There are single observations showing variable degree of association of eosinophilic metaplasia with chronic inflammation [3, 11]. Cheng et al. describe eosinophilic metaplasia as a lesion that is frequently encountered in inflammatory conditions, suggesting a host response to an altered cellular milieu [6]. Gaudin P et al. describe eosinophilic metaplasia in benign prostate in 32% of the patients with post-radiation therapy for prostatic carcinoma, in close association with chronic inflammation [6]. We published two case reports revealing the association of chronic prostatic inflammation (nonspecific granulomatous prostatitis) with eosinophilic metaplasia in TURP-material [4, 5]. In the present study, we find a very common combination of eosinophilic metaplasia with other types of PEM, most commonly eith the urothelial metaplasia (50%) and BCH (70.6%).

Conclusion

Epithelial metaplasia is in general the result of an adaptive replacement of the cells sensitive to noxious environmental agents by other cells more capable of withstanding such injury [16]. Selecting histologically investigated by us patients (neither radiation and hormonal treatment nor prostatic surgery before TURP), our results indicate that the main pathogenetic factors for PEM are acute and chronic prostate inflammation and BPH. The expression of p63 by all types of PEM and BCH, as well as the frequent combination between them is in favour of stress factors, the transitional zone of the prostate glands increases due to the proliferation of p63+ basal progenitor stem cells. Similar to Barrett's oesophagus molecular pathogenesis, it could be speculated that there is an activation of specific transcription factors leading to the expression of an different metaplastic-type of genes which gives rise to PEM [10]. When the new genotype is more specific – squamous and urothelial metaplasias (direct metaplasia) are likely to develop, and when it is differentiated in a direction other than normal, mucinous or eosinophilic metaplasias (indirect, phenotypical type of metaplasia) develop [13].

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